COPRECIPITATES AND MELTS

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INTRODUCTION

The bioavailability of a poorly water-soluble drug is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution. The effect of the particle size of a drug on its dissolution rate and its biological activity is well known. For example, Atkinson et al. (1) reported that micronization of griseofulvin resulted in reduction of the therapeutic dose by half.

The conventional methods for reducing particle size and increasing surface area include trituration, grinding, ball milling, fluid energy micronization, and controlled precipitation (2). Coprecipitates and melts are solid dispersions that provide a means of reducing particle size to the molecular level. Sekiguchi and Obi (3) first introduced the concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs in 1961. They demonstrated that the eutectic of sulfathiazole and the physiologically inert water–soluble carrier urea exhibited higher absorption and excretion after oral administration than sulfathiazole alone. Recent work on solid dispersions has been extended to the development of sustained–release preparations.

DEFINITIONS AND METHODS OF PREPARATION

Definitions

Chiou and Riegelman (2) defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting–solvent method." Dispersions obtained through the fusion process are often called melts, and those obtained by the solvent method are frequently referred to as coprecipitates or coevaporates. Examples include sulfathiazole–providone (PVP; 4) and reserpine PVP (5).

Methods of Preparation

The two basic procedures used to prepare solid dispersions are the fusion and cosolvent techniques. Modifications of these methods and combinations of them have also been used (2). Recently, application of supercritical fluid process has been explored to form pharmaceutical solid dispersions (6).

Melting or Fusion Method

This method was first reported by Sekiguchi and Obi (3). A physical mixture of an active agent and a water–soluble carrier is heated until it is melted. The melt is solidified rapidly in an ice bath under vigorous stirring, pulverizing and then sieving. Rapid congealing is desirable because it results in supersaturation of the drug as a result of entrapment of solute molecules in the solvent matrix by instantaneous solidification. The solidification process can be achieved on stainless steel plates attached to a cooling system to favor rapid heat loss. Spray congealing from a modified spray drier onto a cold metal surface has also been used. Products from this process can be obtained in pellet form without the necessity of a grinding step that may alter crystalline modification.

Two advantages of the melt method are its simplicity and its economy, as no solvents are involved. However, the method may not be suitable if the drug or the carrier is unstable at the fusion temperature or evaporates at high temperatures. Succinic acid, for example, used as a carrier for griseofulvin, is quite volatile and partially decomposes by dehydration near its melting point. Such problems can be avoided by melting in a sealed container under vacuum or under an inert gas, such as nitrogen. By proper selection of carrier system and composition, the melting point of a binary system can be much lower than the melting point of either of the components.

Other disadvantages of this method may include the tacky and intractable nature of the resulting solidified melt and irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system.

Solvent Method

Tachibana and Nakamura (7) first used this method to prepare a solid dispersion of β-carotene in PVP by using

chloroform as a cosolvent. The solvent is usually removed by evaporation under reduced pressure at varying temperatures. The choice of solvent and its removal rate are critical to the quality of the dispersion. A mixed solvent system may be used. Some examples of solid dispersions prepared by this method include sulfathiazole-PVP (4), reserpine-PVP (5), reserpine-deoxycholic acid (8) and griseofulvin-PVP (9).

The freeze–drying process has been used to prepare dispersions of ketoprofen (10) and dicumarol (11) in PVP from their ammonical solutions. Similarly, the spray-drying process has been used to prepare dispersions of acetohexamide in PVP (12) and chlorthalidone in pentaerythritol (13).

The major advantage of the solvent method is that thermal decomposition of drugs and carriers associated with the fusion method can be avoided. The disadvantages include the higher cost of preparation, the use of large quantities of solvent and the difficulty in complete removal of solvent, the possible adverse effect of residual solvent, the selection of a common volatile solvent, the difficulty of reproducing crystal forms, and the inability to attain a supersaturation of the solute in the solid system unless the system goes through a highly viscous phase.

Supercritical Fluid Process

Supercritical CO_2 is a good solvent for water-insoluble as well as water-soluble compounds under suitable conditions of temperature and pressure. Therefore, supercritical CO_2 has potential as an alternative for conventional organic solvents used in solvent-based processes for forming solid dispersions due to its favorable properties of being nontoxic and inexpensive. The process developed by Ferro Corporation (14) consists of the following steps: 1) charging the bioactive material and suitable polymer into the autoclave; 2) addition of supercritical CO_2 under precise conditions of temperature and pressure, that causes polymer to swell; 3) mechanical stirring in the autoclave; and 4), rapid depressurization of the autoclave vessel through a computer–controlled orifice to obtain desired particle size. The temperature conditions used in this process are fairly mild (35–75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins.

CLASSIFICATION OF SOLID DISPERSIONS

Chiou and Riegelman (2) classified solid dispersions into the following six representative types: 1) simple eutectic mixtures; 2) solid solutions; 3) glass solutions and glass suspensions; 4) amorphous precipitations in a crystalline carrier; 5) compound or complex formation; and 6) combinations of the previous five types. Many techniques have been used to characterize the physical nature of solid dispersions. These include thermal analysis (e.g., cooling-curve, thaw-melt, differential scanning calorimetry and x-ray diffraction, microscopic, spectroscopic, dissolution rate, and thermodynamic methods) Usually, a combination of two or more methods is required to obtain a complete picture of the solid dispersion system.

Simple Eutectic Mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility but negligible solid–solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus, the x-ray diffraction pattern of a eutectic constitutes an additive composite of the two components. A phase diagram of a two-component system is shown in Fig. 1. Examples of this type include phenacetin-phenobarbital (15), chloramphenicol-urea (2), griseofulvin-succinic acid (16), paracetamol-urea, and the dispersions of griseofulvin and tolbutamide in polyethylene glycol-(PEG-2000; 17).

Solid Solutions

In a solid solution, the two components crystallize together in a homogeneous one-phase system. The particle size of

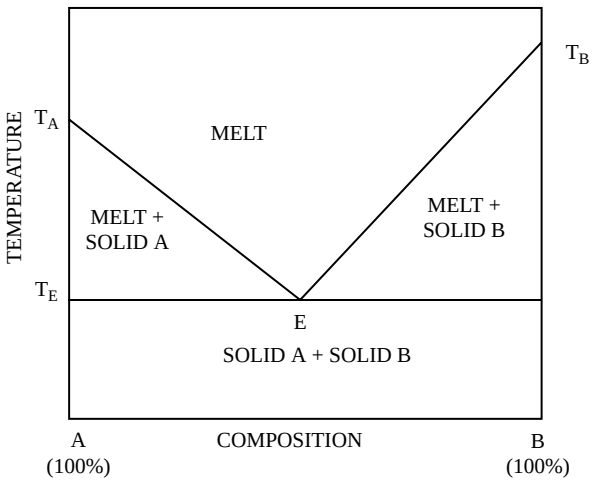

Fig. 1 Simple binary-phase diagram with eutectic formation. T_A is melting point of pure A; T_B is melting point of pure B; and E is eutectic point.

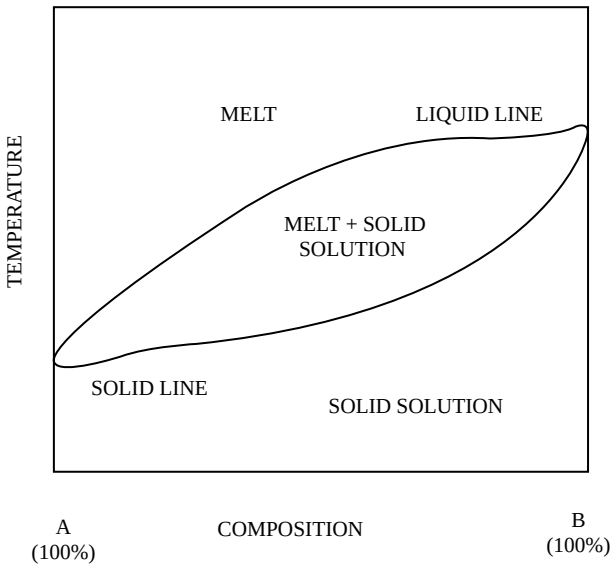

Fig. 2 A phase diagram of continuous solid solution for a binary system A and B.

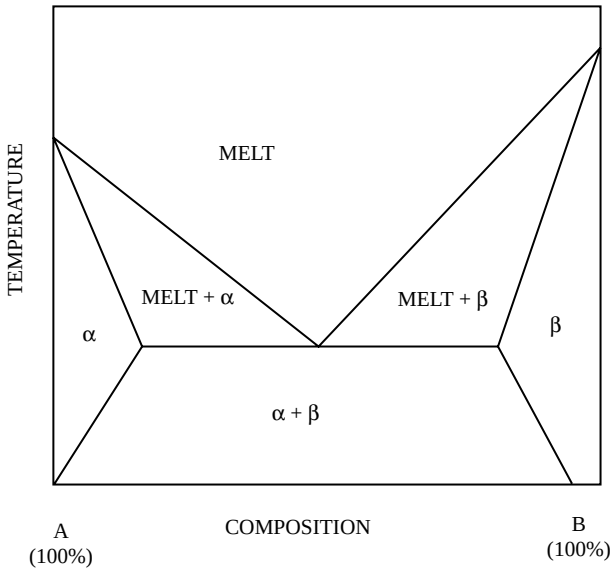

Fig. 3 A typical phase diagram of a discontinuous solid solution for a binary system A and B; α and β are regions of solid solution formation.

the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture.

Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in the solid state in all proportions. Typical phase diagrams of continuous and discontinuous solid solutions are shown in Figs. 2 and 3, respectively. Discontinuous solid solutions exist at extremes of composition. In general, some solid-state solubility can be expected for all two-component systems.

According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional or interstitial. In the substitutional type, the solute molecule substitutes for the solvent molecule in the crystal lattice (Fig. 4). The molecular size of the two components should not differ by more than 15%. This class is represented by solid solutions of p-dibromobenzene-p-chlorobromobenzene, anthracene-acenaphthene, and ammonium and potassium thiocyanate.

An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space (Fig. 4) in the solvent (host) lattice. For this to occur, the solute molecule diameter should be less than 0.59 times that of the solvent molecule; therefore, the volume of the solute molecule should be less than 20% of the solvent molecule. Owing to their large molecular size, polymers favor the formation of interstitial solid solutions. Examples of this type include solid solutions of digitoxin, methyltestosterone, prednisolone acetate, and hydrocortisone acetate in the matrix of PEG-6000. They all exhibit a fast rate of dissolution.

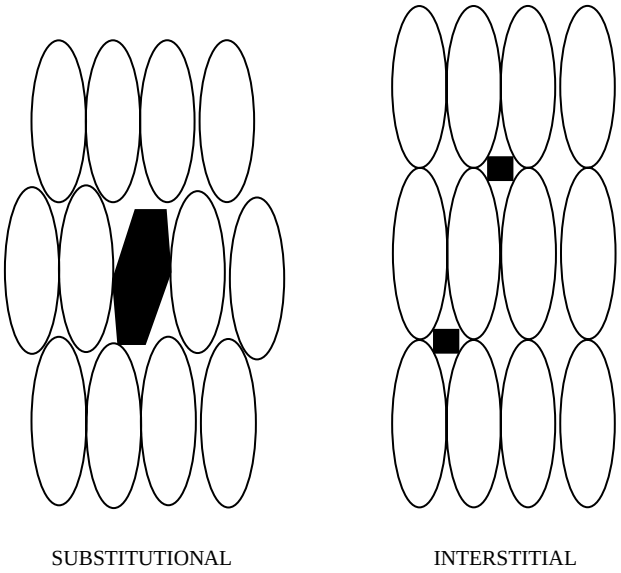

Fig. 4 Schematic representation of substitutional and interstitial solid solutions. Dark symbols represent solute atoms or molecules; open symbols indicate solvent atoms or molecules.

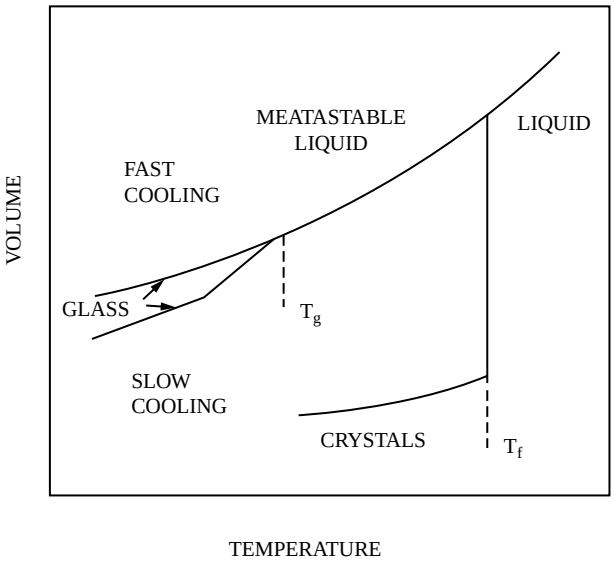

Fig. 5 Volume changes associated with cooling of a melt: T_g is the glass transition temperature and T_f is the melting point of the material.

Glass Solutions and Suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy carrier. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points. Instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. Fig. 5 shows the volume changes associated with glass formation when a melt is cooled down. Examples of carriers that form glass solutions and suspensions include citric acid, sugars such as dextrose, sucrose, and galactose, PVP, urea, and PEG.

Amorphous Precipitations in a Crystalline Carrier

This type of solid dispersion is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous form. In a simple eutectic mixture, the drug is precipitated out in a crystalline form. An example of this is the precipitation of sulfathiazole in the amorphous form in crystalline urea (3). It is postulated that a drug with a propensity to supercooling has more tendency to solidify as an amorphous form in the presence of a carrier.

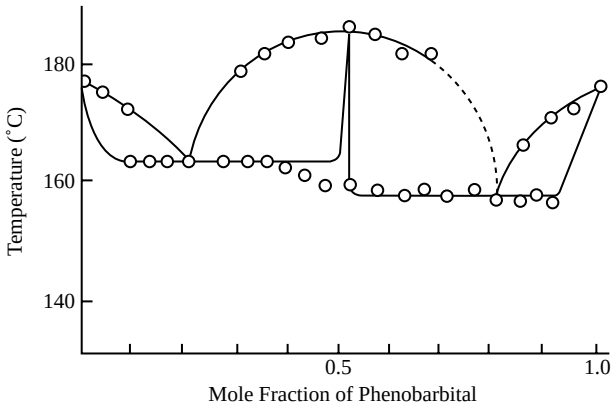

Fig. 6 Quinine-phenobarbital system, showing molecular compound formation. (Reproduced from Ref. 15. Copyright the American Pharmaceutical Association.)

Compound or Complex Formation

When two substances form a molecular compound, it usually gives rise to a maximum in the phase diagram. An example of this is the quinine-phenobarbital system (15) shown in Fig. 6. It is difficult to generalize the influence of complex formation on dissolution. A complex between digoxin and hydroquinone exhibited a high dissolution rate (16), whereas the insoluble complex between phenobarbital and PEG was shown to reduce both the rates of dissolution and the permeation of phenobarbital through everted rat gut (17).

MECHANISM OF INCREASED DISSOLUTION RATE

The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400-fold (18) to less than twofold. Corrigan (19) reviewed the current understanding of the mechanism of release from solid dispersions. The increase in dissolution rate for solid dispersions can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution of these systems are as follows:

1. Reduction of particle size. In the case of glass, solid solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area solubilization.

2. Solubilization effect. The carrier material, as it dissolves, may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea, as well as for numerous other drugs (20).
3. Wetability and dispersibility. The carrier material may also have an enhancing effect on the wetability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.
4. Metastable forms. Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide was 17 kcal per mol, whereas that for 1:2 furosemide: PVP coprecipitate was only 7.3 kcal per mol (21).

RECENT ADVANCES

Serajuddin (22) reviewed recent advances in solid dispersion technology with particular emphasis on self-emulsifying systems. The advances in filling solid dispersion directly into hard gelatin capsules and availability of surface active and self-emulsifying carriers have renewed interest in commercial development of drug products based on solid dispersion. For ease of manufacturing, the carrier must be amenable to liquid filling into hard gelatin capsules as melts. The melting temperatures of carriers should be such that the solutions do not exceed approximately 70°C, which is the maximum acceptable temperature for hard gelatin capsule melts. Two such surface-active carriers that are being explored in solid dispersions for the bioavailability enhancement are Gelucire 44/14 (Gattfosse Corp, France) and Vitamin E TPGS NF (Eastman, Kingsport, TN). Gelucire 44/14 is a mixture of glyceryl and PEG-1500 esters of long chain fatty acids (lauryl macrogolglycerides). The suffixes 44 and 14 refer to its melting point and HLB value respectively. Serajuddin et al. also has shown that appropriate combinations of polysorbate 80 and PEG yield self-emulsifying systems.

SUSTAINED-RELEASE SOLID DISPERSIONS

More recently, the concept of solid dispersions has been explored using insoluble carrier materials. These systems are suitable for formulating sustained-release dosage forms. Hasegawa et al. (23, 24) prepared sustained-release dosage forms of nifedipine by forming solid dispersions with anionic polymers, such as hydroxypropylmethyl cellulose phthalate and methacrylic acid-methacrylic acid methyl ester copolymers. Nifedipine in these solid dispersions was amorphous and was practically insoluble in gastric fluid (pH 1.2). However, it dissolved rapidly in intestinal fluid (pH 6.8) and showed a supersaturation phenomenon. These solid dispersions provided sustained absorption of nifedipine in beagle dogs with good availability after oral administration. Stability studies indicated that these dispersions were stable for at least 6 months under accelerated conditions. Similar dispersions of digoxin and dipyridamole (25) also showed delayed absorption with good bioavailability. Moreover, the chemical stability of digoxin in acidic medium was improved.

Fassihi et al. (26) used a combination of hydrophilic and lipophilic polymers to control the release rate. Thus, solid dispersions of theophylline were prepared by the fusion method using various ratios of PEG-6000, ethyl cellulose, and acrylic/methacrylic esters.

Takahashi et al. (27) showed that the coprecipitates of cationic water-soluble drugs (e.g., thioridazine hydrochloride), with pectin can be used as sustained-release preparations.

Controlled-release formulations of acetaminophen, aminopyrine, chlorpheniramine maleate, and salicylic acid that use Eudragit RSPM as a water-insoluble carrier, prepared by the solvent method, have been reported (28). A novel approach that uses a less soluble derivative of the drug as a carrier was used by Yang and Swarbrick (29) to prepare sustained-release solid dispersions of dapsone.

SELECTION OF A CARRIER

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug: 1) be freely water-soluble with intrinsic rapid dissolution properties; 2) be nontoxic and pharmacologically inert; 3) be heat stable with a low melting point for the melt method; 4) be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method; 5) be able to, preferably, increase the aqueous solubility of the drug; and 6) be chemically compatible with the drug and not form a strongly bonded complex with the drug.

Table 1 Materials used as carriers for solid dispersions

Sugars: Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
Acids: Citric acid, succinic acid
Polymeric materials: Povidone (PVP), polyethylene glycols (PEG), hydroxypropyl-methylcellulose, methylcellulose, hydroxyethylcellulose, cyclodextrins, hydroxypropylcellulose, pectin, galactomannan
Insoluble or enteric polymers: Hydroxypropylmethylcellulose phthalate, Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS
Surfactants: Polyoxyethylene stearate, Renex, Poloxamer 188, Texafor AIP, deoxycholic acid, Tweens, Spans
Miscellaneous: Pentaerythritol, pentaerythrityltetracetate, urea, urethane, hydroxyalkylxanthins.

(Adapted from Ref. 19).

Table 1 shows a list of materials used as carriers for solid dispersion formation. An excellent review of many of these carriers is included in an article by Ford (30). Enteric polymers are useful in the formation of solid dispersions of acid labile drugs. In some cases, a combination of carriers is more useful.

ADVANTAGES AND DISADVANTAGES OF SOLID DISPERSIONS

Among the advantages of solid dispersions are the rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic metabolism. This latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug, as in the case of 17-β-estradiol (31); or inhibition of the enzyme by the carrier, as in the case of morphine-tristearin dispersion (32). Both can lead to the need for lower doses of the drug. Other advantages include transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG-6000 to give a solid (33), avoidance of polymorphic changes and thereby bioavailability problems, (as in the case of nabilone and PVP dispersion (34), and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption (35).

The major disadvantages of solid dispersions are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market (36). Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersions may not lend themselves to easy handling because of tackiness.

REVIEW OF IN VIVO STUDIES

Several examples of in vivo performance of solid dispersions have been published. The in vivo performance of solid dispersion systems containing sulfathiazole-urea, chloramphenicol-urea, reserpine-bile acids, and griseofulvin-PEGs were reviewed by Chiou and Riegelman (2). Some other representative examples are summarized below:

1. Nifedipine. Solid dispersions of nifedipine with PVP (37) and enteric polymers (23, 24) were evaluated in dogs and humans. PVP dispersions showed rapid absorption with a threefold increase in bioavailability when compared to physical mixtures. Sustained blood levels were obtained from solid dispersions with enteric polymers.
2. Acetaminophen. The effect of aging of the solid dispersion of acetaminophen in PEG-20,000 on human bioavailability was studied (38). It was found that the bioavailability of the sample stored at room temperature for 9 months decreased. This was due to an increase in the crystallinity of the drug.
3. Phenytoin. Solid dispersions of phenytoin in PEG-4000 (39), PEG-6000 (40), and PVP (41) were evaluated in vivo. The total areas under blood concentration curve (AUC) after oral administration to human volunteers were fourfold greater from a 1:10 PEG-4000 dispersion and 2.7-fold greater from a physical mixture than from phenytoin crystals. PEG-6000 dispersions (40% drug) were examined in mixed-breed dogs and compared with phenytoin sodium. Although phenytoin sodium dissolved several times faster in vitro than the solid dispersion of phenytoin, the two preparations were found to be bioequivalent. Sekikawa et al. (41) studied absorption of phenytoin in humans from PVP dispersions. The extent of bioavailability of phenytoin in phenytoin-PVP coprecipitate was 1.54 times greater than that of phenytoin alone.
4. Nitrofurantoin. Nitrofurantoin dispersed in PVP, PEG, and mannitol was evaluated in humans by studying cumulative urinary excretion of the drug (42). A linear

correlation was found between the amount of nitrofurantoin dissolved in acidic medium after 30 and 90 minutes and the cumulative amount of unchanged drug excreted after 12 h. The bioavailability relative to pure drug was 239% for a 1:4 PVP dispersion, 190% for a 1:4 PEG-6000 dispersion and 150% for a 1:10 mannitol dispersion. Stoll et al. (43) studied the absorption characteristics of various nitrofurantoin and nitrofurantoin-deoxycholic acid preparations. The l:5 (w/w) nitrofurantoin-deoxycholic acid dispersion showed significant increases in both the rate and extent of absorption when compared with either the drug alone or the physical mixture.

5. Dicumarol. Sekikawa et al. (11) used the rabbit as a model to evaluate the performance of solid dispersions of dicumarol in PVP and β-cyclodextrin. Peak levels of the drug were observed at 4–6 h postadministration in the cases of the solid dispersion systems. In the case of dicumarol crystal powder, peak levels were observed at 2 to 12 hours postadministration. Average AUC values (0–48 h) of dicumarol following the administration of the dicumarol-PVP solid dispersion systems were 3.31 times (coevaporation method) and 1.54 times (freeze-drying method) that of control. The corresponding numbers for β-cyclodextrin dispersions were 2.18 and 1.72.
6. HIV Protease Inhibitor. The bioavailability of ritonavir (Norvir, Abbott), an HIV protease inhibitor, was enhanced by formulation as a solid dispersion in a mixture of surface active carrier, such as Gelucire 50/13, polysorbate 80, and polyoxyl-35 castor oil.

FUTURE OF SOLID DISPERSIONS

In spite of tremendous research activity in the area of solid dispersion since its introduction to pharmaceutic applications in 1961, only a few systems, such as Gris-PEG (Sandoz), a griseofulvin-PEG solid dispersion, Cesamet (Lilly), a nabilone-PVP solid dispersion, Sporanox capsules (Janssen), an itraconazole-HPMC solid dispersion, and Norvir capsules (Abbott), are identified as such in the market place. Most likely many others are utilized but masked as formulation methods. Perhaps the limited commercial utilization of the concept stems in part from the instability of solid dispersions on aging and the need for a high content of carrier, which might restrict its use to very potent drugs for physical and economic reasons. Nevertheless, solid dispersions have great potential both for increasing the bioavailability of drugs and for developing controlled-release preparations.

In regard to manufacturing considerations, the problem of total solvent removal in dispersions prepared by the solvent method needs to be addressed. The method created by Hasegawa et al. (23), which involves spray coating of nonpareils or any other inert core with drug-carrier solution, provides a one-step process of achieving a multiunit dosage form of solid dispersions. With particle-coating equipment now commercially available (44), this process has a promising future, as exemplified by commercial success of Sporanox capsules manufactured by this technique (45).

The problem of instability of the supersaturated state upon dissolution, which results in a stable form, has been dealt with by addition of a retarding agent. Methyl cellulose was used as a retarding agent in dispersions of indomenhacin and flufenamic acid in PVP (46, 47). Computer optimization of such compositions, as described by Takayama, et al. (47), will certainly be of great value. More work is needed in these areas.

Novel formulating methods can provide cleaner manufacturing conditions. For example, Walker et al. (48) demonstrated the feasibility of liquid-filling gelatin capsules with the liquid melt and avoiding grinding-induced changes in crystallinity. This would be a very attractive feature for potent drug candidates. Exploration for new carrier systems will certainly continue. The most commonly used carriers are polymers, such as PVP and PEG. Recently lipids (49), freeze-dried milk (50), and self-emulsifying agents (22) have been used as carriers. Finally, the emergence of considerable research on novel drug-delivery systems may provide the greatest impetus for increased use of solid dispersions. Valuable preliminary studies of the use of solid dispersions to provide sustained- or controlled-release of drugs (23–27) have been reported. A U.S. patent (51) describes a method of preparation for a controlled release preparation of cyclosporine in biodegradable polymer, such as poly-D,L-lactide or a blend of poly-D,L-lactide and poly-D,L-lactide-*co*-glycolide. More and more commercial applications are expected in this area.

REFERENCES

1. Atkinsons, R.M.; Bedford, C.; Child, K.J.; Tomich, E. Antibiot. Chemother. **1962**, *12*, 232–238.
2. Chiou, W.L.; Riegelman, S. J. Pharm. Sci. **1971**, *60*, 1281–1302.
3. Sekiguchi, K.; Obi, N. Chem. Pharm. Bull. **1961**, *9*, 866–872.
4. Simonelli, A.P.; Mehta, S.C.; Higuchi, W.I. J. Pharm. Sci. **1969**, *58*, 538–549.

5. Bates, T.R. J. Pharm. Pharmacol. **1969**, *21*, 710–712.
6. Ye, C.; Frank, S. AAPS Annual Meeting Abstract. 1988.
7. Tachibana, T.; Nakamura, A. Kolloid-Z. Polym. **1965**, *203*, 130–133.
8. Malone, M.H.; Hochman, H.I.; Nieforth, K.A. J. Pharm. Sci. **1966**, *55*, 972–974.
9. Mayersohn, M.; Gibaldi, M. J. Pharm. Sci. **1966**, *55*, 1323–1324.
10. Takayama, K.; Nambu, N.; Nagai, T. Chem. Pharm. Bull. **1982**, *30*, 3013–3016.
11. Sekikawa, H.; Fukyda, W.; Takada, M.; Ohtani, K.; Arita, T.; Nakano, M. Chem. Pharm. Bull. **1983**, *31*, 1350–1356.
12. Graf, E.; Beyer, C.; Abdallah, O. Acta Pharm. Technol. **1982**, *8*, 225.
13. Bloch, D.W.; Elegakey, M.A.; Speiser, P. Pharm. Acta Helv. **1983**, *58*, 14–22.
14. Ferro Corporation, Independence, Ohio. Company Literature on Ferro Process™ Using Supercitical Fluid Technology.
15. Guillory, J.K.; Hwang, S.C.; Lach, J.L. J. Pharm. Sci. **1969**, *58*, 301–308.
16. Bochner, F.; Huffman, D.H.; Shen, D.D.; Azarnoff, D.L. J. Pharm. Sci. **1977**, *66*, 644–647.
17. Singh, P.; Guillory, J.K.; Sokolosky, T.D.; Benet, L.Z.; Bhatia, V.N. J. Pharm. Sci. **1966**, *55*, 63–68.
18. Said, S.A.; Fatatry, H.M.; Geneidi, A.S. Aust. J. Pharm. Sci. **1974**, *53*, 42–45.
19. Corrigan, O.I. Drug Dev. Ind. Pharm. **1985**, *11*, 697–724.
20. Roseman, M.; Jencks, W.P. J. Amer. Chem. Soc. **1975**, *97*, 631–640.
21. Shin, S.C. Arch., Pharm. Res. **1979**, *2*, 35.
22. Serajuddin, A.T.M. J. Pharm. Sci. **1999**, *88*, 1058–1066.
23. Hasegawa, A.; Nakagawa, H.; Sugimoto, I. Chem. Pharm. Bull. **1985**, *33*, 1616–1619.
24. Hasegawa, A.; Nakagawa, H.; Sugimoto, I. Chem. Pharm. Bull. **1985**, *33*, 388–391.
25. Hasegawa, A.; Kawamura, R.; Nakagawa, H.; Sugimoto, I. Chem. Pharm. Bull. **1986**, *34*, 2183–2190.
26. Fassihi, A.R.; Parker, M.S.; Pourkavoos, N. Drug Dev. Ind. Pharm. **1985**, *11*, 523–535.
27. Takahashi, Y.; Nambu, N.; Nagai, T. Chem. Pharm. Bull. **1986**, *34*, 327–332.
28. Athanikar, N. Diss. Abstr. Int. B 1978 **1977**, *38* (10), 4740–4741.
29. Yang, T.T.; Swarbrick, J. J. Pharm. Sci. **1986**, *75*, 53–56, 264–270.
30. Ford, J.L. Pharm. Acta Helv. **1986**, *61*, 69–88.
31. Resetarits, D.E.; Cheng, K.C.; Bolten, B.A.; Prasad, P.A.; Shefter, E.; Bates, T.R. Int. J. Pharm. **1973**, *2*, 113–123.
32. Chang, K.S.; Jarowski, C.I. J. Pharm. Sci. **1980**, *69*, 466–469.
33. Chiou, W.L.; Smith, L.D. J. Pharm. Sci. **1971**, *60*, 125–127.
34. Thakkar, A.; Hirsh, C.A.; Page, J.G. J. Pharm. Pharmacol. **1977**, *29*, 783–784.
35. Halpern, A.; Bradney, C.H. US Patent 2,698,822,1955.
36. *Abbott to Substitute Norvir Capsules with Liquid Formulation;* Abbott Laboratories, 1998; press release, July 29.
37. Sugimoto, I.; Kuchiki, A.; Nakagawa, H.; Tohgo, K.; Kondo, S.; Iwane, I.; Takahashi, K. Drug Dev. Ind. Pharm. **1980**, *6*, 137–160.
38. Vila, Jato, J.L.; Vlanco, J.; Martinez, R.; Concheiro, A. *Biopharmaceutics Pharmacokinetics, Second European Congress*; Aiache, J.M., Hirtz, J., Eds.; Lavoisier: Paris France, 1984; 353–359.
39. Yakou, S.; Umehara, K.; Sonobe, T.; Nagai, T.; Sugihara, M.; Fukuyama, Y. Chem. Pharm. Bull. **1984**, *32*, 4130–4136.
40. Stavchansky, S.; Gowan, W.G. J. Pharm. Sci. **1984**, *73*, 733–736.
41. Sekikawa, H.; Fujiwara, J.; Naganuma, T.; Nakano, M.; Arita, T. Chem. Pharm. Bull. **1978**, *26*, 3033–3039.
42. Ali, A.A.; Gorashi, A.S. Int. J. Pharm. **1984**, *19*, 297–306.
43. Stoll, R.G.; Bates, T.R.; Swarbrick, J. J. Pharm. Sci. **1973**, *62*, 65–68.
44. Mehta, A.M.; Valazza, M.J.; Abele, S.E. Pharm. Technol. **1986**, *10* (4), 46–56.
45. Gilis, P.; De Conde, M.V.;Valentin, F.V.; Vandecruys, R.P.G. US Patent 5,633,015, May 27, 1997.
46. Takayama, K.; Nambu, N.; Nagai, T. Chem. Pharm. Bull. **1983**, *31*, 4496–4507.
47. Takayama, K.; Imaizumi, H.; Nambu, N.; Nagai, T. Chem. Pharm. Bull. **1985**, *33*, 292–300.
48. Walker, S.E.; Ganley, J.A.; Bedford, K.; Eaves, T. J. Pharm. Pharmacol. **1980**, *32*, 389–393.
49. Venkatram, S.; Rogers, J.A. Drug Dev. Ind. Pharm. **1985**, *11*, 223–238.
50. Macheras, P.E.; Reppas, C.I. J. Pharm. Sci. **1986**, *75*, 692–696.
51. Zeibun, R. US Patent 5,641,745, June 24, 1997.